PRODUCT MONOGRAPH

HUMULIN® R

(insulin, human biosynthetic)

Solution for Injection, 100 units/mL

HUMULIN® N

(insulin isophane, human biosynthetic, rDNA origin)

Suspension for Injection, 100 units/mL

HUMULIN® 30/70

(30% insulin injection, 70% insulin isophane, human biosynthetic, rDNA origin)

Suspension for Injection, 100 units/mL

THERAPEUTIC CLASSIFICATION

Anti-Diabetic Agent

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Control № 167827

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HUMULIN® R

(insulin, human biosynthetic)

HUMULIN® N

(insulin isophane, human biosynthetic, rDNA origin)

HUMULIN® 30/70

(30% insulin injection, 70% insulin isophane, human biosynthetic, rDNA origin)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Parenteral	Solution for Injection/ 100 units/mL	**HUMULIN R (Regular)**: Glycerol, m-cresol, water for injection, hydrochloric acid and sodium hydroxide.
	Suspension for Injection/ 100 units/mL	**HUMULIN-N (NPH)** and **HUMULIN 30/70** also contain phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

INDICATIONS AND CLINICAL USE

HUMULIN (insulin, human biosynthetic) is indicated for the treatment of insulin requiring diabetic patients.

HUMULIN-R only should be used for the treatment of emergencies such as diabetic coma and pre-coma and in diabetics undergoing surgery, but not HUMULIN-N, or HUMULIN MIXTURES.

In switching patients from animal source insulins to HUMULIN, it is possible that the patients will require a change in dosage; the adjustment may be made with the first dose or over a period of several weeks. Any change of insulin should be made cautiously and only under medical supervision.

Changes in refinement, purity, strength, brand, type and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage.

CONTRAINDICATIONS

HUMULIN (insulin, human biosynthetic) is contraindicated during episodes of hypoglycemia.

HUMULIN is contraindicated in patients with hypersensitivity to human insulin or any of its excipients contained in the formulation (unless used as part of a desensitization program).

HUMULIN-N, HUMULIN MIXTURES, should not be given intravenously or used for treatment of diabetic coma.

WARNINGS AND PRECAUTIONS

General

Serious Warnings and Precautions

Hypoglycemia is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death (see OVERDOSAGE, Symptoms and Treatment).

Any transfer of HUMULIN or HUMULIN MIXTURES should be made cautiously and only under medical supervision (see DOSAGE AND ADMINISTRATION).

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control (see DOSAGE AND ADMINISTRATION).

HUMULIN and HUMULIN MIXTURES should not be mixed with any other insulin unless clearly indicated and done under medical supervision (see DOSAGE AND ADMINISTRATION).

Under no circumstances should any HUMULIN MIXTURE be given intravenously.

Do not use the HUMULIN-N or HUMULIN MIXTURES if you see lumps that float or that stick to the sides of the vial, or if the contents of the vial are clear and remain clear after the bottle is shaken or rotated. NOTE: The contents of the vial or cartridge of HUMULIN-R should be clear. Do not use if cloudy.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

As with all insulin therapies, the duration of action of HUMULIN and HUMULIN MIXTURES may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Hypokalemia is among the potential clinical adverse effects associated with the use HUMULIN and all other insulin therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhea).

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose (see Part III – Consumer Information).

To avoid transmission of disease, a cartridge or prefilled syringe should not be used by more than one person.

The number and size of daily doses and the time of administration, as well as diet and exercise, are problems that require direct and continuous medical supervision. Usually, the most satisfactory injection time is before breakfast.

Insulin plus Thiazolidinediones (TZDs): TZDs, alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph Warnings and Precautions information when the use of these drugs in combination with any insulin, including HUMULIN R, HUMULIN N or HUMULIN 30/70, is contemplated.

Transferring Patients from Other Insulins

When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may change or become less pronounced than those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g., regular, NPH, or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first few weeks or months and under medical supervision (see WARNINGS AND PRECAUTIONS).

Carcinogenesis and Mutagenesis

Human insulin is produced by recombinant technology. No serious events have been reported in subchronic toxicology studies. Human insulin was not mutagenic in a battery of in vitro and in vivo genetic toxicity assays (see TOXICOLOGY).

Endocrine and Metabolism

Hypoglycemia

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapies, including HUMULIN. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death (see ADVERSE REACTIONS).

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see OVERDOSAGE).

Hypoglycemia can occur regardless of the type of insulin taken and may cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions or loss of consciousness. In extreme circumstances, even death can occur without recognizable symptoms.

In certain cases (e.g., long duration of diabetes mellitus, diabetic nerve disease, intensified diabetes mellitus control, patients with psychiatric illness, elderly patients or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycemia (pallor, sweating, anxiety, headache, tachycardia, hunger) may change or be less pronounced.

Hypoglycemic reactions following treatment with HUMULIN are mostly mild and easily managed.

Changes in insulin therapy or changes in life style (i.e., diet, exercise/physical activity) may require a change in dosage to avoid hypoglycemia. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Glucose monitoring is recommended for all patients with diabetes mellitus who are also taking HUMULIN or other insulin products (see Monitoring and Laboratory Tests).

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery) especially in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

Diabetic patients should be instructed to carry a few lumps of sugar, candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur (see Part III, CONSUMER INFORMATION).

Hyperglycemia

Inadequate dosing or discontinuation of HUMULIN, especially in type 1 diabetes mellitus, may lead to hyperglycemia and when untreated, hyperglycemic events may eventually lead to diabetic ketoacidosis or coma which are potentially fatal. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include polydipsia; polyuria; nausea; abdominal pain, vomiting; drowsiness; blurred vision, flushed dry skin; loss of appetite, weight loss as well as acetone odour of breath (see ADVERSE REACTIONS).

Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. This may constitute a risk in situations where these abilities are of special importance such as driving a car or operating machinery.

Hepatic/Biliary/Pancreatic

Insulin requirements may be decreased in the presence of hepatic impairment.

Immune

Local Allergic Reactions:

With insulin therapies including HUMULIN, patients may experience redness, swelling, pain, inflammation, or itching at the site of injection (see ADVERSE REACTIONS). Prompt recognition and appropriate management of the allergic complications of insulin therapy are important for the safe and effective control of diabetes mellitus.

Most of these minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients (see CONTRAINDICATIONS).

Rarely, subcutaneous (SC) administration of insulin products including HUMULIN can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions.

Systemic Allergic Reactions:

Systemic allergic reactions have rarely occurred with insulin treatments including HUMULIN. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop in blood pressure (see ADVERSE REACTIONS).

Severe cases of generalized allergy including anaphylactic reaction may be life threatening (see CONTRAINDICATIONS).

Antibody Production:

Immune responses can occur with insulin products, including production of auto antibodies (IgG). In general, glycemic control is not affected by the presence of auto antibodies. Very rarely, auto antibodies may cause hyperglycemia (insulin resistance) or hypoglycemia (inappropriate release). Insulin antibodies are frequently cross-reactive. Patients who have demonstrated an allergic reaction to other insulin products may demonstrate an allergic reaction to HUMULIN.

Renal

Insulin requirements may be decreased in the presence of renal impairment.

Reproduction Studies

There are no adequate and well-controlled studies with HUMULIN during pregnancy and lactation (see TOXICOLOGY).

Information for Patients

Patients should be informed about potential advantages and disadvantages of HUMULIN therapy, including possible side effects. Patients should also be offered continued education and advice on insulin therapies, delivery device options, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, and instruction for use of injection devices, storage of insulin, travelling and others (see PART III: CONSUMER INFORMATION).

Female patients with diabetes mellitus should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health is essential in pregnant patients with diabetes (see Special Populations and PART III: CONSUMER INFORMATION).

Special Populations

Pregnant Women

HUMULIN may be used in pregnancy, if clinically indicated. It is essential to maintain good glucose control in both gestational diabetes and throughout pregnancy in type 1 and type 2 patients. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters.

Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy.

Nursing Women

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Pediatrics (<18 years of age)

HUMULIN may be used in children and adolescents, if clinically indicated.

Geriatrics (>65 years of age)

HUMULIN may be used in elderly patients, if clinically indicated.

Monitoring and Laboratory Tests

Self-Monitoring of Blood Glucose

With insulin therapy, including HUMULIN, the need for regular blood glucose self-monitoring should be considered to obtain optimal glycemic control (see PART III: CONSUMER INFORMATION). Glycosylated hemoglobin should be measured every 3 to 4 months in all patients taking insulin products.

ADVERSE REACTIONS

Body as a Whole – Allergic reaction(s)

Local allergy in patients may occur as redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy to insulin is less common but potentially more serious. Generalized allergy to insulin may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse or sweating. Severe cases of generalized allergic reaction may be life-threatening.

Skin and appendages – Lipodystrophy

Insulin lipohypertrophy has been reported with HUMULIN. This complication has been ascribed to the local pharmacologic effects of the subcutaneous injection of insulin. A few cases of lipoatrophy and serum sickness have also been reported.

Metabolic – Hypoglycemia; Insulin resistance

Hypoglycemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycemia may lead to loss of consciousness and, in extreme cases, death.

DRUG INTERACTIONS

Drug-Drug Interactions

Insulin requirements may be decreased in the presence of agents such as oral antidiabetic medications, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-adrenergic blockers, alcohol, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and anabolic steroids.

Drugs that may increase insulin requirements include oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics and danazol. The hypoglycemic action of insulin may also be antagonized by diphenylhydantoin.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

Hormones that tend to counteract the hypoglycemic effects of insulin include growth hormone, corticotropin, glucocorticoids, thyroid hormone, and glucagon. Epinephrine not only inhibits the secretion of insulin, but also stimulates glycogen breakdown to glucose. Thus, the presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

Insulin plus Thiazolidinediones (TZDs): To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia (see WARNINGS AND PRECAUTIONS and OVERDOSAGE).

DOSAGE AND ADMINISTRATION

Dosing Considerations

New Patients:

Patients receiving insulin for the first time can be started on HUMULIN (insulin, human biosynthetic) in the same manner as they would be on animal-source insulin.

Patients should be monitored closely during the adjustment period.

Transfer Patients:

When transferring patients from animal-source insulin to HUMULIN, use the same dose and dosage schedule.

Some patients transferring to HUMULIN will require a change in dosage from that used with animal-source insulin. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.

Changes in total daily dosage, the number of injections per day, and/or timing of injections may be necessary to achieve maximum glycemic control.

When a patient on high doses of animal insulin is switched to HUMULIN, it may be appropriate to reduce the starting dosage and monitor the patient carefully.

Patients who have systemic allergy to pork or beef insulin may also react to human insulin. In such patients, appropriate procedures (intradermal testing and, if necessary, desensitization) should be undertaken before therapeutic doses of human insulin are administered.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that the early warning symptoms, i.e., nervousness, sweating, and palpitations, were less pronounced than they were with animal-source insulin.

Formulations of HUMULIN appear to produce a slightly faster onset and slightly shorter duration of action than the corresponding forms of animal-source insulins.

Recommended Dose and Dosage Adjustment

The dosage should be determined by the physician, according to the requirements of the patient.

HUMULIN-R is a clear, colourless solution. It may be administered by subcutaneous, intramuscular or intravenous injection.

HUMULIN-N and HUMULIN MIXTURES are suspensions. They should be administered by subcutaneous injection only.

Subcutaneous administration, preferably by the patient, should be in the upper arms, thighs, buttocks or abdomen. Injection sites should be rotated so that the same site is not used more than approximately once a month.

Care should be taken to ensure that a blood vessel has not been entered. The injection site should not be massaged.

Administration

Mixing Instructions:

The short action of HUMULIN-R is preserved when mixed with HUMULIN-N; independent of the time lag between mixing and administration, and independent of the proportion of regular insulin incorporated in the mixture.

The effects of mixing HUMULIN with animal-source insulins have not been studied. This practice is not recommended.

OVERDOSAGE

Hypoglycemia (low blood glucose, also called "insulin reaction") can occur if the patient takes too much insulin, misses meals, exercises or works too hard just before a meal, or has an infection or becomes ill (especially with diarrhea or vomiting) or if the body's need for insulin change for other reasons.

Symptoms and Treatment

Hypoglycemia may occur in any patient receiving insulin and is most commonly manifested by hunger, nervousness, warmth and sweating, and palpitations. Patients also may experience headache, confusion, drowsiness, fatigue, anxiety, blurred vision, diplopia, or numbness of the lips, nose, or fingers. The clinical manifestations of hypoglycemia can be masked by the concomitant administration of propranolol or other beta adrenergic blockers.

If a patient is unable to take soluble carbohydrate or fruit juice orally, hypoglycemia is treated with 10 to 20 g of dextrose intravenously or glucagon may be given subcutaneously or intramuscularly.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Insulin, human biosynthetic, is a polypeptide hormone consisting of a 21 amino acid A-chain and a 30 amino acid B-chain linked by two disulfide bonds. HUMULIN (insulin, human biosynthetic) is found to be chemically, physically, biologically and immunologically equivalent to pancreatic human insulin which differs slightly from porcine or bovine insulin in amino acid composition.

Studies indicate that immunogenicity problems with biosynthetic human insulin (BHI) produced by recombinant DNA technology are less likely than with insulin that is derived from animal origin. Biosynthetic human insulin is devoid of all protein contaminants of pancreatic origin normally present in trace amounts in all insulins of pancreatic origin. The purification procedures used in the manufacture of biosynthetic human insulin result in a product which contains an insufficient quantity of E. coli polypeptides to be antigenic in deliberately sensitized animals. No antibodies to E. coli polypeptides have been detected in specifically designed radioimmunoassay methods examining patient serum samples.

Mechanism of Action

The administration of suitable doses of insulin to patients with diabetes mellitus, along with controlled diet and exercise, temporarily restores their ability to metabolize carbohydrates, fats and proteins; to store glycogen in the liver; and to convert glucose to fat. When given in suitable doses at regular intervals to a patient with diabetes mellitus, the blood sugar is maintained within a reasonable range, the urine remains relatively free of sugar and ketone bodies, and diabetic acidosis and coma are prevented.

Pharmacodynamics

The primary activity of human insulin is the regulation of glucose metabolism. In addition, insulin has several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Pharmacokinetics

Insulin preparations differ in onset, peak and duration of action. Individual variations of blood glucose response profiles are dependent upon factors such as the size of dose, site of injection and physical activity of the patient (for all human insulin formulations). The addition of protamine to insulin, in the presence of zinc, produces a stable complex with less intense and more prolonged action, due to its slow dissolution.

HUMULIN-R, insulin injection, human biosynthetic (rDNA Origin) REGULAR is a short-acting insulin with a duration of activity of 6 to 8 hours.

HUMULIN-N, insulin isophane, human biosynthetic (rDNA Origin) NPH is an intermediate-acting insulin with a slower onset of action than Regular insulin and a longer duration of activity of up to 24 hours.

HUMULIN MIXTURE, insulin injection, insulin isophane, human biosynthetic (rDNA Origin) 30/70 is an intermediate-acting insulin with a more rapid onset of action than NPH alone and a duration of activity of up to 24 hours.

HUMULIN-N may be mixed with HUMULIN-R to meet individual metabolic requirements of the patient as determined by the physician.

STORAGE AND STABILITY

Prior to first use insulin should be stored in a cold place (2-8°C), preferably in a refrigerator, but not in a freezer. Do not let it freeze or leave it in direct sunlight. Expiration dates are stated on the labels.

When in current use, vials, cartridges and prefilled pens should be stored at room temperature and discarded after 28 days.

SPECIAL HANDLING INSTRUCTIONS

See Part III CONSUMER INFORMATION for injection procedures for vials and instructions for use of cartridges/ pens. Also refer to the User Manual for HUMULIN KwikPen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HUMULIN is available in the following presentations:

HUMULIN R, insulin injection, human biosynthetic (rDNA Origin) REGULAR:

- Vial HI0210, 10 mL, 100 units/mL.
- Vial HI0213, 3 mL, 100 units/mL.
- Cartridge HI0219, 3.0 mL, 100 units/mL, 5 cartridges/box.

HUMULIN R KwikPen™, insulin injection, human biosynthetic (rDNA Origin) REGULAR:

- Cartridge and Pen HP8804, 3.0 mL prefilled pen, 100 units/mL, 5 pens/box.

HUMULIN N, insulin isophane, human biosynthetic (rDNA Origin) NPH:

- Vial HI0310, 10 mL, 100 units/mL.
- Vial HI0313, 3 mL, 100 units/mL.
- Cartridge HI0319, 3.0 mL, 100 units /mL, 5 cartridges/box.

HUMULIN N KwikPen™, insulin isophane, human biosynthetic (rDNA Origin) NPH:

- Cartridge and Pen HP8805, 3.0 mL prefilled pen, 100 units/mL, 5 pens/box.

HUMULIN 30/70, 30% insulin injection, 70% insulin isophane, human biosynthetic (rDNA Origin):

- Vial HI0710, 10 mL, 100 units/mL.
- Cartridge HI0719, 3.0 mL, 100 units /mL, 5 cartridges/box.

HUMULIN cartridges are designed for use with Lilly injector systems.

Not all pack sizes and presentations may be marketed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

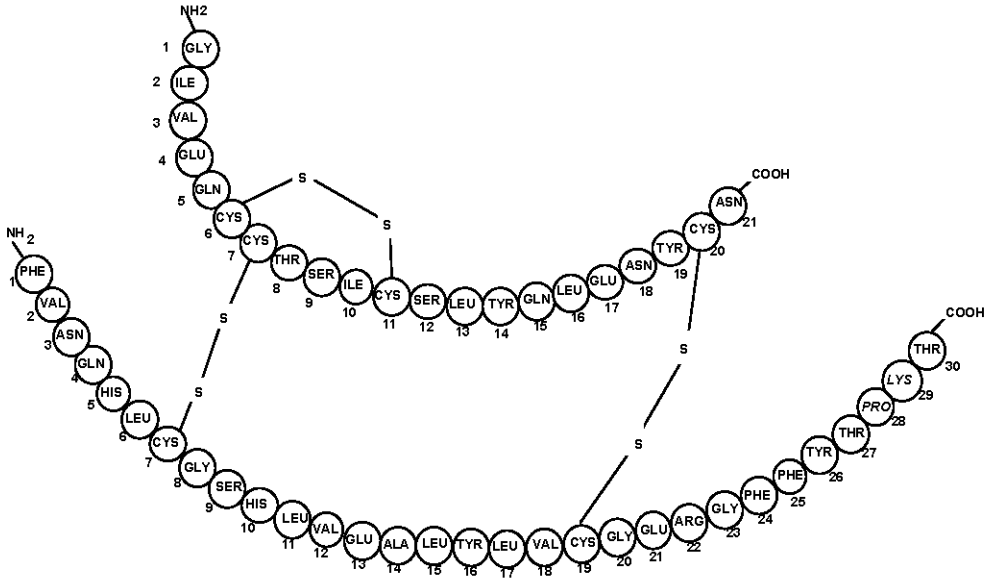
Drug Substance

HUMULIN (insulin, human biosynthetic) is a polypeptide hormone consisting of a 21 amino acid A-chain and a 30 amino acid B-chain linked by two disulfide bonds. It is synthesized in a non-disease-producing special laboratory strain of E. coli that has been genetically altered by the addition of the human gene for insulin production.

Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_6$

Molecular weight: 5807.72.

Structural formula:



CLINICAL TRIALS

New Patient Studies

One hundred and twenty nine (129) insulin naive patients were treated for one year. Dramatic, albeit expected, improvement of metabolic control followed institution of biosynthetic human insulin (BHI). Insulin antibody binding was measured and compared with results obtained from a well-matched group of historical controls on animal insulins. BHI was less immunogenic than modified beef pork (MBP) or purified pork insulin (PPI). The possible reasons that BHI is ever immunogenic in humans are (1) the fact that BHI is given subcutaneously and (2) the presence of insulin aggregates.

Transfer Patient Studies

In a double-blind, double-crossover study, patients were switched from beef-insulin to PPI or BHI and then back again; patients on BHI had modestly higher fasting blood sugars. Moreover, the A.M. dose of BHI could be administered closer to breakfast than was possible with animal-sourced insulins.

In another double-blind study, patients were switched either to BHI or maintained on their PPI or MBP insulin. Patients switched from MBP or PPI to BHI had slightly higher fasting and/or postprandial blood sugars than control groups which were maintained on their prestudy animal insulin programs. Patients switched from MBP to BHI demonstrated clear reductions in their serum insulin antibody binding. Patients switched from PPI to BHI demonstrated significantly less insulin binding at six months after transfer; at 24 months, bound insulin was essentially the same for both groups.

The immune responses of a subset of 142 of 427 transfer patients have been statistically analyzed. These patients had been randomly allocated to treatment with BHI, PPI or MBP. Taking type of diabetes into account, this study confirmed that BHI was the least immunogenic.

Use of BHI in Patients with Complications of Insulin Therapy:

In isolated instances where patients were experiencing insulin allergy or resistance to insulin therapy, BHI has been used with limited success.

There are isolated case reports in which patients with the complications of insulin therapy, principally lipoatrophy, insulin allergy and insulin resistance, have been treated with BHI.

Overall, the clinical studies indicate that BHI is an effective, safe insulin both in patients receiving insulin for the first time and in patients being switched from animal insulin. However, BHI appears to be shorter acting than animal insulin. The data from these studies are not sufficient to determine whether BHI is superior to PPI in the prevention or treatment of complications of insulin therapy. However, HUMULIN (insulin, human biosynthetic) was shown to be less immunogenic than mixed beef-pork insulin or purified pork insulin.

DETAILED PHARMACOLOGY

Preclinical Pharmacology

Biosynthetic human insulin (BHI) has been studied extensively. In nearly all the studies, BHI was compared with native pancreatic human insulin as well as with purified pork insulin. The resulting data clearly indicate that BHI is chemically, physically, biologically and immunologically equivalent to the appropriate pancreatic insulin standards. BHI is prepared by the proinsulin route, starting with an *E. coli* fermentation using recombinant DNA-containing plasmids. The amino acid sequences of the insulin chains were found to be correct and the disulfide bonds were shown to be in the proper configuration. Additional chemical and physical studies verified that the normal structure of the human insulin molecule was integrally formed by the proinsulin process.

Further confirmation that BHI is structurally identical to pancreatic human insulin was provided by radioimmunochemical assays for insulin. BHI and pancreatic human insulin reacted identically in the insulin radioimmunoassay, a method that is sensitive to minor structural variations within the insulin molecule.

The biological activity of BHI was evaluated by a wide variety of in vitro techniques, all of which demonstrated that BHI and pancreatic human insulin are equivalent within experimental error. In addition, BHI was found to have a hypoglycemic potency equivalent to purified pancreatic insulins as determined by the USP rabbit assay.

BHI did not elicit an antigenic response when administered to *E. coli* polypeptide-sensitized rats and guinea pigs. In a clinical experiment, it was demonstrated that the anti- *E. coli* polypeptide antibody levels in 20 new diabetic patients were the same regardless of whether the treatment was with BHI or purified pork insulin.

No antibodies specific to *E coli* polypeptide have been detected in patient serum samples from over 1,350 patients.

Clinical Pharmacology

Clinical pharmacologic studies with, biosynthetic human insulin (rDNA) demonstrate that generally the pharmacokinetics and pharmacodynamics of BHI and purified pork insulin (PPI) are the same. However, serum concentrations after BHI is administered subcutaneously may be higher or occur sooner than after PPI. These differences are generally ascribed to the greater solubility of BHI, which apparently is related to the presence of threonine instead of alanine on the $B\text{-}_{30}$ position of the molecule.

A 30/70 Regular/NPH mixture produced the same effect as equivalent doses of the two formulations administered separately. Mixtures of NPH and Regular BHI have demonstrated a slight excess of protamine in NPH BHI which binds to added Regular insulin, and that this binding delays slightly the occurrence of the peak serum concentration. Effects of BHI on substrates and other non-insulin and glucose parameters have been studied. Most investigators

have reported that the suppression of endogenous insulin as indicated by serum C-peptide values was equivalent for BHI and PPI.

Growth hormone (GH) increase was also equivalent or slightly less with BHI. Prolactin response was less after BHI than with PPI, while the cortisol response to insulin hypoglycemia may be greater with BHI than with PPI. There was no difference in non-esterified fatty acid lowering or blood glycerol, lactate, or 3-hydroxybutyrate levels between BHI and PPI.

While the effects of BHI on suppression of human C-peptide usually are the same as those for PPI, BHI may affect other variables differently than PPI. Further studies will be needed to determine the significance of differences between BHI and PPI on prolactin, GH, and glucagon concentrations.

TOXICOLOGY

As with pork insulin, biosynthetic human insulin will be mainly used by subcutaneous injection in humans and, therefore, the majority of studies in animals have been performed using this route of administration. However, acute toxicity studies in monkeys and a subchronic study in dogs were performed using intravenous administration. The experiments for acute toxicity are presented in Table 1 and for subacute toxicity in Table 2 and are summarized as follows:

- The selection of dose levels of human insulin for the single and multiple dose studies in animals was restricted by the potent hypoglycemic activity of this compound. The pharmacological effects of insulin are well-known from many years of human therapy and therefore the toxicological studies were designed to evaluate adverse effects of possible impurities such as *E. coli* polypeptides.
- The minimal lethal subcutaneous dose of biosynthetic human insulin in rats and mice was greater than 10 units/kg. This dose was a large multiple of the initial human clinical trial dose and also much greater than the average daily therapeutic dose of insulin (0.6 units/kg/day).
- Dogs given a single subcutaneous dose of 2 units/kg or an intravenous dose of 0.1 unit/kg of human insulin evidenced hypoglycemia and related pharmacological effects but no significant toxicity.
- No compound-related toxic effects were observed when rats were given daily subcutaneous injections of 2.4 units/kg of biosynthetic human insulin for one month. Similarly, beagle dogs given daily subcutaneous injections of 2 units/kg or intravenous injections of 0.1 unit/kg of human insulin for one month evidenced marked hypoglycemia, but no adverse effects were seen on hematologic or serum chemistry parameters and there were no pathologic changes. There was no evidence of tissue damage or irritation at the site of injection in the rats or dogs.
- Biosynthetic human insulin gave negative results in the Modified Ames, Rat Hepatocyte, and Chinese Hamster mutagenicity tests.

It can be concluded that injections of pharmacologically effective doses of biosynthetic human insulin in animals did not produce toxic effects. There were no findings that would preclude the use of this compound in humans.

Table 1. Acute Toxicity

Species	Number Per Dose	Route	Single Dose	Duration (Days)	Observations
Rats	10 females 10 males	SC	10 IU/kg	14	No mortality. Minimum lethal dose > 10 IU/kg.
Mice	10 females 10 males	SC	10 IU/kg	14	No mortality. Alopecia in females on BHI. Minimum lethal dose > 10 IU/kg.
Mice	10 females 10 males	SC	10 IU/kg	14	No mortality. Minimum lethal dose > 10 IU/kg
Rats	10 females 10 males	SC	10 IU/kg	14	Significant tolerance of doses without signs of toxicity.
Dogs	2 females 2 males	SC	2 IU/kg	14	Significant tolerance of doses without signs of toxicity.
Monkeys	2 females 2 males	IV	1 IU/kg	14	Significant tolerance without signs of toxicity. Blood glucose values decreased sharply in all animals 15-20 minutes post administration.

Table 2. Subacute Toxicity

Species	Number Per Dose	Route	Single Daily Dose	Number of Doses	Observations
Rats	15 females 15 males	SC	2.4 IU/kg/day	30	No toxicologically important changes occurred.
Dogs	3 females 3 males	SC	2.0 IU/kg/day	30	One male on BHI experienced convulsions. Some ataxia and hypoactivity.
Dogs	4 females 4 males	IV	0.1 IU/kg /day	30	Decreased thrombocyte numbers. Minor changes in alanine transaminase activities.

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PART III: CONSUMER INFORMATION

HUMULIN® R CARTRIDGES

insulin injection, human biosynthetic (rDNA origin)

Solution for Injection, 100 units/mL

and HUMULIN® R KWIKPEN™

insulin injection, human biosynthetic (rDNA origin)

Solution for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® R was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® R. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN R (Regular) consists of zinc-insulin crystals dissolved in a clear fluid. HUMULIN R is a short-acting insulin with a duration of activity of 6 to 8 hours.

HUMULIN R cartridges and HUMULIN R KwikPen (prefilled pens) are for subcutaneous (under the skin) injection.

What the medication is used for:

HUMULIN R is a short-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN R should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN R should not be used during episodes of hypoglycemia (too little sugar in the blood).

HUMULIN R should be used only if your doctor has prescribed Regular insulin (insulin injection). You should not attempt to add any insulin to this cartridge.

If HUMULIN N and HUMULIN R mixtures are prescribed, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN R contains insulin, human biosynthetic.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid and sodium hydroxide.

What dosage forms it comes in:

HUMULIN R (Regular) is a sterile solution containing insulin, human biosynthetic (rDNA origin) for injection. It is available in:

- Cartridges, 3 mL
- KwikPens, 3 mL prefilled pen

HUMULIN R is also available in:

- Vials, 3 mL
- Vials, 10 mL

Other available HUMULIN products include HUMULIN N (NPH) and HUMULIN 30/70 (mixture of 30% Regular and 70% NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and cartridge or KwikPen (prefilled pen) label and is followed by the proper letter designation and name for the insulin formulation: R-Regular
2. The carton and the cartridge or KwikPen label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

HUMULIN R should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

The contents of the cartridge of HUMULIN R should be clear. Do not use if cloudy.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN R will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN R and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers, and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INSTRUCTIONS FOR USE

HUMULIN R cartridges are designed for use with Lilly injector systems (reusable pens).

HUMULIN R cartridges and KwikPens (prefilled pens) are not designed to allow any other insulin to be mixed in the cartridge.

HUMULIN R cartridges and KwikPens MUST NOT be refilled and are not designed for use with a traditional syringe.

However, it is recommended that you carry a syringe, so that in the event of an emergency, i.e. pen does not work, you can withdraw insulin from the cartridge for a single use. This cartridge should not be reused as repeated withdrawals may cause the cartridge to break. Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**

For KwikPen users it is also recommended to carry an extra KwikPen in case yours is lost or damaged.

For guidance on the use of the KwikPen (prefilled, disposable pen) please refer to the separate Instructions for Use enclosed within the packaging.

Preparing the Dose:

1. Wash your hands.
2. Always examine the cartridge or KwikPen (prefilled pen) of HUMULIN R after removing from the box. HUMULIN R should be clear and colourless. DO NOT use HUMULIN R if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible or if the cartridge or KwikPen is cracked or broken.
3. Carefully load the cartridge into the reusable pen following the manufacturer's directions.
4. Wipe the exposed rubber membrane on the metal cap end of the cartridge or KwikPen (prefilled pen) with an alcohol swab and attach the needle.
5. Prime the pen as directed by the manufacturer. If air bubbles are present, hold the pen with the needle pointing up and tap the side of the pen until the bubbles float to the top. With the pen still vertical, purge the needle with a 2 unit dose setting of the pen. Repeat until an insulin drop appears at the end of the needle. There may be small bubbles left; the air is harmless but too large an air bubble will affect the accuracy of the insulin dose administered.
6. Set the dose as instructed by your doctor. A gauge has been provided on the side of the cartridge to help you judge the amount of insulin remaining. The distance between each mark represents approximately 20 units for 3 mL cartridges or KwikPens.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made. To avoid tissue damage, always change the site for each injection by at least 1.5 cm (0.5 inches) from the previous site, rotating sites on the body.
2. Insert the needle under the skin, as you were taught. **Do not** inject directly into a vein.
3. To inject the insulin, follow the instructions of the pen's manufacturer.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. Immediately after injection, remove the needle from the pen. This will ensure sterility and prevent leakage, re-entry of air and potential needle clogs.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN R is for subcutaneous (under the skin) injection. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal

- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN R, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN R cartridges or KwikPens (prefilled pens) should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The cartridge or KwikPen of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. The cartridge of insulin currently in use should be left in the pen and may be carried with you. Cartridges or KwikPens in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of Cartridge:
HUMULIN R should be clear and colourless. DO NOT USE a cartridge or KwikPen of HUMULIN R if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A cartridge or KwikPen that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

Last revised: October 22, 2013

PART III: CONSUMER INFORMATION

HUMULIN® R VIALS

insulin injection, human biosynthetic (rDNA origin)

Solution for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® R was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® R. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN R (Regular) consists of zinc-insulin crystals dissolved in a clear fluid. It is a short-acting insulin with a duration of activity of 6 to 8 hours.

HUMULIN R vials are for subcutaneous (under the skin) injection.

What the medication is used for:

HUMULIN R is a short-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood to various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN R should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN R should not be used during episodes of hypoglycemia (too little sugar in the blood).

HUMULIN R should be used only if your doctor has prescribed Regular insulin (insulin injection).

If HUMULIN N and HUMULIN R mixtures are prescribed, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN R contains insulin, human biosynthetic.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid and sodium hydroxide.

What dosage forms it comes in:

HUMULIN R (Regular) is a sterile solution containing insulin, human biosynthetic (rDNA origin) for injection. It is available in:

- Vials, 3 mL
- Vials, 10 mL

HUMULIN R is also available in:

- Cartridges, 3 mL
- KwikPens, 3 mL prefilled pen

Other available HUMULIN products include HUMULIN N (NPH) and HUMULIN 30/70 (mixture of 30% Regular and 70% NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and vial and is followed by the proper letter designation and name for the insulin formulation: R-Regular.
2. The carton and the vial label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

HUMULIN R should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

The contents of the vial of HUMULIN R should be clear. Do not use if cloudy.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN R will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN R and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers, and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INJECTION PROCEDURES FOR VIALS

Correct Syringe

Doses of insulin are measured in units. U-100 insulin contains 100 units/mL. It is important to use a syringe that is marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED**. **Follow the package directions supplied with your syringe**.

Preparing the Dose:

1. Wash your hands.
2. Always examine the vial of HUMULIN R after removing from the box. HUMULIN R should look clear and colourless. DO NOT use HUMULIN R if it appears cloudy, thickened, or slightly coloured or if solid particles are visible, or if the vial is cracked or broken.
3. If using a new bottle (vial), flip off the plastic protective cap, but do not remove the stopper. Wipe the top of the vial with an alcohol swab.
4. If you are mixing insulins, follow the instructions for mixing given to you by your doctor or nurse.
5. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin vial and inject the air into the vial.
6. Turn the vial and syringe upside down. Hold the vial and syringe firmly in 1 hand.
7. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.
8. Before removing the needle from the vial, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe needle up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
9. Remove the needle from the vial and lay the syringe down so that the needle **does not touch anything**.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made.
2. Inject under the skin, as you were taught. **Do not** inject directly into a vein.
3. Push the plunger in as far as it will go.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue damage, give the next injection at a site at least 1.5 cm (0.5 inches) from the previous site.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN R is for subcutaneous (under the skin) injection. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal
- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN R, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN R vials should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The vial of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. Vials in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of the Vial:

HUMULIN R should be clear and colourless. DO NOT USE a vial of HUMULIN R if it appears cloudy, thickened, or slightly coloured or if solid particles are visible. A vial that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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Last revised: October 22, 2013

PART III: CONSUMER INFORMATION

HUMULIN® N CARTRIDGES

insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

and HUMULIN® N KWIKPEN™

insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® N was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® N. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN N – NPH (insulin isophane, human biosynthetic, rDNA origin) has been modified so that it has a different duration of action than Regular insulin. The result is an intermediate-acting insulin with a slower onset of action than Regular insulin and a longer duration of activity of up to 24 hours.

HUMULIN N cartridges and HUMULIN N KwikPen (prefilled pens) are for subcutaneous (under the skin) injection only.

What the medication is used for:

HUMULIN N is an intermediate-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN N should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN N should not be used during episodes of hypoglycemia (too little sugar in the blood).

HUMULIN N should not be given intravenously or used for treatment of diabetic coma.

HUMULIN N should be used only if your doctor has prescribed NPH insulin (insulin isophane). You should not attempt to add any insulin to this cartridge or KwikPen (prefilled pen).

If HUMULIN N and HUMULIN R mixtures are prescribed, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN N contains insulin isophane, human biosynthetic.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid, sodium hydroxide, phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

What dosage forms it comes in:

HUMULIN N (NPH) is a sterile suspension containing insulin isophane, human biosynthetic (rDNA origin) for subcutaneous injection. It is available in:

- Cartridges, 3 mL
- KwikPens, 3 mL prefilled pen

HUMULIN N is also available in:

- Vials, 3 mL
- Vials, 10 mL

Other available HUMULIN products include HUMULIN R (Regular) and HUMULIN 30/70 (mixture of 30% Regular and 70% NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and cartridge or KwikPen (prefilled pen) label and is followed by the proper letter designation and name for the insulin formulation: N-NPH.
2. The carton and cartridge or KwikPen label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

HUMULIN N should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

Do not use HUMULIN N if you see lumps that float or that stick to the sides of the cartridge, or if the contents of the cartridge are clear and remain clear after the bottle is shaken or rotated.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN N will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN N and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INSTRUCTIONS FOR USE

HUMULIN N cartridges are designed for use with Lilly injector systems (reusable pens).

HUMULIN N cartridges and KwikPens (prefilled pens) are not designed to allow any other insulin to be mixed in the cartridge.

HUMULIN N cartridges and KwikPens MUST NOT be refilled and are not designed for use with a traditional syringe. However, it is recommended that you carry a syringe, so that in the event of an emergency, i.e. pen does not work, you can withdraw insulin from the cartridge for a single use. This cartridge should not be reused as repeated withdrawals may cause the cartridge to break. Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**

For KwikPen users it is also recommended to carry an extra KwikPen in case yours is lost or damaged.

For guidance on the use of the KwikPen (prefilled, disposable pen) please refer to the separate Instructions for Use enclosed within the packaging.

Preparing the Dose:

1. Wash your hands.
2. Always examine the cartridge or KwikPen (prefilled pen) of HUMULIN N after removing from the box. Re-suspend the insulin by rolling the cartridge or KwikPen between your palms 10 times and inverting it 180° 10 times. HUMULIN N should look uniformly cloudy or milky after mixing. If not, repeat the re-suspension procedure as often as necessary. DO NOT USE if the white insulin particles stick to the bottom or sides of the cartridge or KwikPen or if there are clumps floating in the insulin, or if the cartridge or KwikPen is cracked or broken.
3. Carefully load the cartridge into the reusable pen following the manufacturer's directions.
4. Wipe the exposed rubber membrane on the metal cap end of the cartridge or KwikPen (prefilled pen) with an alcohol swab and attach the needle.
5. Carefully re-suspend the HUMULIN N by rolling the cartridge and pen in your hands 10 times and inverting it 180° 10 times. This must be performed each time before you give yourself an injection even after just loading the pen.
6. Prime the pen as directed by the manufacturer. If air bubbles are present, hold the pen with the needle pointing up and tap the side of the pen until the bubbles float to the top. With the pen still vertical, purge the needle with a 2 unit dose setting of the pen. Repeat until an insulin drop appears at the end of the needle. There may be small bubbles left; the air is harmless but too large an air bubble will affect the accuracy of the insulin dose administered.
7. Set the dose as instructed by your doctor. A gauge has been provided on the side of the cartridge to help you judge the amount of insulin remaining. The distance between each mark represents approximately 20 units for 3 mL cartridges or KwikPens.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made. To avoid tissue damage, always change the site for each injection by at least 1.5 cm (0.5 inches) from the previous site, rotating sites on the body.
2. Insert the needle under the skin, as you were taught. **Do not** inject directly into a vein.
3. To inject the insulin, follow the instructions of the pen's manufacturer.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. Immediately after injection, remove the needle from the pen. This will ensure sterility and prevent leakage, re-entry of air and potential needle clogs.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN N is for subcutaneous (under the skin) injection only. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control,

patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal
- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions

to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN N, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN N cartridges or KwikPens (prefilled pens) should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The cartridge or KwikPen of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. The cartridge of insulin currently in use should be left in the pen and may be carried with you. Cartridges or KwikPens in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of Cartridge/KwikPen:

DO NOT USE a cartridge or KwikPen of HUMULIN N if after re-suspending, there are clumps floating in the insulin, or if solid white particles stick to the bottom or wall of the cartridge giving it a frosted appearance (re-suspend the insulin by following instruction 2 under Preparing the Dose). A cartridge or KwikPen that appears frosted or contains clumps, or is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

Last revised: October 22, 2013

PART III: CONSUMER INFORMATION

HUMULIN® N VIALS

insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® N was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® N. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN N – NPH (insulin isophane, human biosynthetic, rDNA origin) has been modified so that it has a different duration of action than Regular insulin. The result is an intermediate-acting insulin with a slower onset of action than Regular insulin and a longer duration of activity of up to 24 hours.

HUMULIN N vials are for subcutaneous (under the skin) injection only.

What the medication is used for:

HUMULIN N is an intermediate-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN N should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN N should not be used during episodes of hypoglycemia (too little sugar in the blood).

HUMULIN N should not be given intravenously or used for treatment of diabetic coma.

HUMULIN N should be used only if your doctor has prescribed NPH insulin (insulin isophane).

If HUMULIN N and HUMULIN R mixtures are prescribed, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN N contains insulin isophane, human biosynthetic.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid, sodium hydroxide, phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

What dosage forms it comes in:

HUMULIN N (NPH) is a sterile suspension containing insulin isophane, human biosynthetic (rDNA origin) for subcutaneous injection. It is available in:

- Vials, 3 mL
- Vials, 10 mL

HUMULIN N is also available in:

- Cartridges, 3 mL
- KwikPens, 3 mL prefilled pen

Other available HUMULIN products include HUMULIN R (Regular) and HUMULIN 30/70 (mixture of 30% Regular and 70% NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and vial label and is followed by the proper letter designation and name for the insulin formulation: N-NPH.
2. The carton and the vial label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

HUMULIN N should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

Do not use HUMULIN N if you see lumps that float or that stick to the sides of the vial, or if the contents of the vial are clear and remain clear after the bottle is shaken or rotated.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN N will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN N and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers, and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INJECTION PROCEDURES FOR VIALS

Correct Syringe

Doses of insulin are measured in units. U-100 insulin contains 100 units/mL. It is important to use a syringe that is marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED**. **Follow the package directions supplied with your syringe**.

Preparing the Dose:

1. Wash your hands.
2. Always examine the bottle (vial) of HUMULIN N after removing from the box. Carefully shake or rotate the insulin vial several times to completely mix (or re-suspend) the insulin. HUMULIN N should look uniformly cloudy or milky after mixing. If not, repeat the re-suspension procedure as often as necessary until the contents are mixed. DO NOT USE if the white insulin particles stick to the bottom or sides of the vial or if there are clumps floating in the insulin or if the vial is cracked or broken.
3. If using a new bottle (vial), flip off the plastic protective cap, but do not remove the stopper. Wipe the top of the vial with an alcohol swab.
4. If you are mixing insulins, follow the instructions for mixing that were given to you by your doctor or nurse.
5. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin vial and inject the air into the vial.
6. Turn the vial and syringe upside down. Hold the vial and syringe firmly in 1 hand.
7. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.
8. Before removing the needle from the vial, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe needle up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
9. Remove the needle from the vial and lay the syringe down so that the needle **does not touch anything**.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made.
2. Insert the needle under the skin, as you were taught. **Do not** inject directly into a vein.
3. Push the plunger in as far as it will go.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue damage, give the next injection at a site at least 1.5 cm (0.5 inches) from the previous site.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN N is for subcutaneous (under the skin) injection only. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal

- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN N, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN N vials should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The vial of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. Vials in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of the Vial:

DO NOT USE a vial of HUMULIN N if after re-suspending, there are clumps floating in the insulin, or if solid white particles stick to the bottom or wall of the vial giving it a frosted appearance (re-suspend the insulin by following instruction 2 under Preparing the Dose). A vial that appears frosted or contains clumps, or is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

Last revised: October 22, 2013

PART III: CONSUMER INFORMATION

HUMULIN® 30/70 CARTRIDGES

30% insulin injection, human biosynthetic and 70% insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® 30/70 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® 30/70. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN 30/70 is a fixed mixture of 30% HUMULIN R-Regular (insulin injection, human biosynthetic) and 70% HUMULIN N- NPH (insulin isophane, human biosynthetic). It is an intermediate-acting insulin with a more rapid onset of action than NPH insulin alone. The duration of activity may last up to 24 hours following injection.

HUMULIN 30/70 cartridges are for subcutaneous (under the skin) injection only.

What the medication is used for:

HUMULIN 30/70 is a combination of an intermediate-acting and a short-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN 30/70 should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN 30/70 should not be used during episodes of hypoglycemia (low blood sugar).

HUMULIN 30/70 should not be given intravenously or used for treatment of diabetic coma.

HUMULIN 30/70 should be used only if your doctor has prescribed insulins mixed in a ratio of 30% REGULAR and 70% NPH. You should not attempt to change the ratio of these products by adding additional NPH or REGULAR insulin to this cartridge.

If HUMULIN N and HUMULIN R mixtures are prescribed in a different proportion, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN 30/70 contains 30% HUMULIN R and 70% HUMULIN N.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid, sodium hydroxide, phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

What dosage forms it comes in:

HUMULIN 30/70 is a sterile suspension containing 30% insulin injection (Regular) and 70% insulin isophane (NPH), human biosynthetic (rDNA origin), for subcutaneous injection only. It is available in:

- Cartridges, 3 mL

HUMULIN 30/70 is also available in:

- Vials, 10 mL

Other available HUMULIN products include HUMULIN R (Regular) and HUMULIN N (NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and cartridge label and is followed by the proper letter designation and name for the insulin formulation: 30/70: 30% insulin injection, 70% insulin isophane, human biosynthetic (rDNA) origin.
2. The carton and the cartridge label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

HUMULIN 30/70 should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

Under no circumstances should HUMULIN 30/70 be given intravenously.

Do not use HUMULIN 30/70 if you see lumps that float or that stick to the sides of the cartridge, or if the contents of the cartridge are clear and remain clear after the cartridge is shaken or rotated.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN 30/70 will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN 30/70 and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INSTRUCTIONS FOR USE

HUMULIN 30/70 cartridges are designed for use with Lilly injector systems (reusable pens).

HUMULIN 30/70 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

HUMULIN 30/70 cartridges MUST NOT be refilled and are not designed for use with a traditional syringe. However, it is recommended that you carry a syringe so that in the event of an emergency, i.e. pen does not work, you can withdraw insulin from the cartridge for a single use. This cartridge should not be reused as repeated withdrawals may cause the cartridge to break. Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**

Preparing the Dose:

1. Wash your hands.
2. Always examine the cartridge of HUMULIN 30/70 after removing from the box. Re-suspend the insulin by rolling the cartridge between your palms 10 times and inverting it 180° 10 times. HUMULIN 30/70 should look uniformly cloudy or milky after mixing. If not, repeat the re-suspension procedure as often as necessary. DO NOT USE if the white insulin particles stick to the bottom or sides of the cartridge or if there are clumps floating in the insulin, or if the cartridge is cracked or broken.
3. Carefully load the cartridge into the reusable pen following the manufacturer's directions.
4. Wipe the exposed rubber membrane on the metal cap end of the cartridge with an alcohol swab and attach the needle.
5. Carefully re-suspend the HUMULIN 30/70 by rolling the cartridge and pen in your hands 10 times and inverting it 180° 10 times. This must be performed each time before you give yourself an injection even after just loading the pen.
6. Prime the pen as directed by the manufacturer. If air bubbles are present, hold the pen with the needle pointing up and tap the side of the pen until the bubbles float to the top. With the pen still vertical, purge the needle with a 2 unit dose setting of the pen. Repeat until an insulin drop appears at the end of the needle. There may be small bubbles left; the air is harmless but too large an air bubble will affect the accuracy of the insulin dose administered.
7. Set the dose as instructed by your doctor. A gauge has been provided on the side of the cartridge to help you judge the amount of insulin remaining. The distance between each mark represents approximately 20 units for 3 mL cartridges.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made. To avoid tissue damage, always change the site for each injection by at least 1.5 cm (0.5 inches) from the previous site, rotating sites on the body.
2. Insert the needle under the skin, as you were taught. **Do not** inject directly into a vein.
3. To inject the insulin, follow the instructions of the pen's manufacturer.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. Immediately after injection, remove the needle from the pen. This will ensure sterility and prevent leakage, re-entry of air and potential needle clogs.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN 30/70 is for subcutaneous (under the skin) injection only. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal
- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of

these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN 30/70, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN 30/70 cartridges should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The cartridge of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. The cartridge of insulin currently in use should be left in the pen and may be carried with you. Cartridges in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of the Cartridge:

DO NOT USE a cartridge of HUMULIN 30/70 if after re-suspending there are clumps floating in the insulin or if solid white particles stick to the bottom or wall of the cartridge giving it a frosted appearance (re-suspend the insulin by following instruction 2 under Preparing the Dose). A cartridge that appears frosted or contains clumps, or is cracked or broken, should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$Report online at www.healthcanada.gc.ca/medeffect
$Call toll-free at 1-866-234-2345
$Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

Last revised: October 22, 2013

PART III: CONSUMER INFORMATION

HUMULIN® 30/70 VIALS

30% insulin injection, human biosynthetic and 70% insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® 30/70 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® 30/70. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN 30/70 is a fixed mixture of 30% HUMULIN R- Regular (insulin injection, human biosynthetic) and 70% HUMULIN N- NPH (insulin isophane, human biosynthetic). It is an intermediate-acting insulin with a more rapid onset of action than NPH insulin alone. The duration of activity may last up to 24 hours following injection.

HUMULIN 30/70 vials are for subcutaneous (under the skin) injection only.

What the medication is used for:

HUMULIN 30/70 is a combination of an intermediate-acting and a short-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN 30/70 should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN 30/70 should not be used during episodes of hypoglycemia (low blood sugar).

HUMULIN 30/70 should not be given intravenously or used for treatment of diabetic coma.

HUMULIN 30/70 should be used only if your doctor has prescribed insulins mixed in a ratio of 30% REGULAR and 70% NPH. You should not attempt to change the ratio of these products by adding additional NPH or REGULAR insulin to this vial.

If HUMULIN N and HUMULIN R mixtures are prescribed in a different proportion, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN 30/70 contains 30% HUMULIN R and 70% HUMULIN N.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid, sodium hydroxide,phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

What dosage forms it comes in:

HUMULIN 30/70 is a sterile suspension containing 30% insulin injection (Regular) and 70% insulin isophane (NPH), for subcutaneous injection. It is available in:

- Vials, 10 mL

HUMULIN 30/70 is also available in:
- Cartridges, 3 mL

Other available HUMULIN products include HUMULIN R (Regular) and HUMULIN N (NPH).These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and vial label and is followed by the proper letter designation and name for the insulin formulation: 30/70: 30% insulin injection, 70% insulin isophane, human biosynthetic (rDNA) origin.
2. The carton and the vial label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

HUMULIN 30/70 should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

Under no circumstances should HUMULIN 30/70 be given intravenously.

Do not use HUMULIN 30/70 if you see lumps that float or that stick to the sides of the vial, or if the contents of the vial are clear and remain clear after the cartridge is shaken or rotated.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN 30/70 will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. Always keep on hand an extra supply of insulin, as well as a spare needle. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN 30/70 and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fliud retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers, and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INJECTION PROCEDURES FOR VIALS

Correct Syringe

Doses of insulin are measured in units. U-100 insulin contains 100 units/mL. It is important to use a syringe that is marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable syringes and needles should be used only once and then discarded. **NEEDLES AND SYRINGES MUST NOT BE SHARED**. **Follow the package directions supplied with your syringe**.

Preparing the Dose:

1. Wash your hands.
2. Always examine the bottle (vial) of HUMULIN 30/70 after removing from the box. Carefully shake or rotate the insulin vial several times to completely mix (or re-suspend) the insulin. HUMULIN 30/70 should look uniformly cloudy or milky after mixing. If not, repeat the re-suspension procedure as often as necessary until the contents are mixed. DO NOT USE if the white insulin particles stick to the bottom or sides of the vial or if there are clumps floating in the insulin or if the vial is cracked or broken.
3. If using a new bottle (vial), flip off the plastic protective cap, but do not remove the stopper. Wipe the top of the vial with an alcohol swab.
4. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin vial and inject the air into the vial.
5. Turn the vial and syringe upside down. Hold the bottle and syringe firmly in 1 hand.
6. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.
7. Before removing the needle from the vial, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe needle up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
8. Remove the needle from the vial and lay the syringe down so that the needle **does not touch anything**.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made.
2. Inject under the skin, as you were taught. **Do not** inject directly into a vein.
3. Push the plunger in as far as it will go.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue damage, give the next injection at a site at least 1.5 cm (0.5 inches) from the previous site.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN 30/70 is for subcutaneous (under the skin) injection only. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal
- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN 30/70, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN 30/70 vials should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The vial of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. Vials in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of the Vial:

DO NOT USE a vial of HUMULIN 30/70 if after re-suspending there are clumps floating in the insulin or if solid white particles stick to the bottom or wall of the vial giving it a frosted appearance (re-suspend the insulin by following instruction 2 under Preparing the Dose). A vial that appears frosted or contains clumps, or is cracked or broken, should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE. REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

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Last revised: October 22, 2013